prosecution of the application. In no way should this act be viewed as Applicants' acceptance of or acquiescence to the position articulated in the Office Action, or of the lack of any belief that Applicants' arguments in the 23 July response are in fact sufficient to overcome the rejections. Applicants continue to believe and suggest that their arguments are proper and a correct recitation of the law. As further evidence of the strength of Applicants' belief, the subject matter that is now being cancelled from the claims with be prosecuted in a continuation application.

In view of the cited language being moved to another application for prosecution on the merits, Applicants respectfully request reconsideration of the rejections noted in paragraphs 10 and 11 of the Office Action.

Regarding paragraphs 15 – 20 and the various rejections involving the Thorpe references, the Examiner indicated that she understood and accepted Applicants' arguments regarding the distinction between Applicants' claimed invention and the Thorpe disclosure. However, the Examiner further requested that Applicants specify what claim language excludes Thorpe as a reference against Applicants claims. In claim 12, "inducing activation of the platelets; and thereby allowing a thrombus to form" is uniquely characteristic of Applicants' pathway to thrombus formation, and does not occur in the pathway disclosed and used in Thorpe's patents. Applicants would respectfully suggest that Exhibits 1-3 submitted in the previous response graphically support Applicants argument. Further, Applicants would re-emphasize a statement made in the previous response, namely, that none of the cited references teach the use of platelets to initiate the production of a thrombus.

To further clarify this point, Applicants have added the word "thereby" to claim 12 to show the connection between the platelets and thrombus formation. Reconsideration is respectfully requested.

Finally, in the telephone interview, the examiner raised Thorpe's disclosure at columns 30 and 46 of U.S. Patent 6,093,399. Regarding column 30, Thorpe discloses VEGF as the target. Both the pathway used by Applicants' process and the pathway used by Thorpe's pathway may use VEGF as a target. It is respectfully submitted that this is not pertinent to Applicants' invention. Applicants' claim 12 calls for a "targeting component", i.e., an agent used to bind to a target, not the target itself. Reconsideration is respectfully requested.

Regarding column 46 (lines 19-67) Thorpe essentially describes the use of platelets as a target for Thorpe's *protein* coagulation-based intellectual property. Specifically, lines 43-44 state, "Platelet activation produces membrane alterations that can be recognized by monoclonal antibodies."

Further, Thorpe discloses in lines 52-63 that specific antibodies may be used. Specifically, lines 53-62 state, "Anti-LIBS antibodies have been developed by Frelinger et al (1990; 1991), any one of which may be used to deliver a coagulant to a disease or tumor site in accordance herewith. The murine monoclonal anti-platelet antibodies MA-TSPI-1 (directed against human thrombospondin) and MA-PMI-1, and MA-LIBS-1 (directed against LIBS on human platelet glycoprotein IIb/IIIa) of Dewerchin et (1991) may also be used, as may RUU 2.41 and LIBS-1 of Heynen et al(1994); OP-G2 of Tomiyama et al (1992); and AB-15. Applicants respectfully suggest that in these passages, Thorpe clearly indicates that platelets are the target, not, when activated, the initiator of thrombus formation.

Since Thorpe has defined "activated platelets" as being a component of the tumor stroma (Column 8, lines 6-8), he is clearly describing the use of antibodies as a means of targeting activated platelets within the tumor stroma to deliver the coagulation agent to the tumor. Applicants again respectfully suggest that in these passages, Thorpe clearly indicates that platelets are the target, not the initiator of thrombus formation.

The present invention differs from that described by Thorpe (Column 46) in that applicants are not directing agents to activated platelets *already present* in the tumor stroma (as taught by Thorpe). Instead applicants are purposefully binding platelets to a specific site, inducing platelet activation, and thereby allowing a thrombus to form (claim 12 of the present invention). The formation of the thrombus is initiated by the specific binding of the platelets (induced by agents of the present invention) to the target site. In contrast, Thorpe describes the ability to target activated platelets already found in a specific location; the initiation of clot formation at this site occurs through binding a coagulation factor to the site, not activation of the platelets.

Reconsideration of the various rejections over the cited art are respectfully requested.

During the telephone interview, the Examiner also raised what may be a new issue that Applicants would like to address in this response. The Examiner indicated that the claims call for "administering" and that there may not be any examples or support sufficient to enable this language. In response, Applicants submit the enclosed Rule 132 affidavit that shows that *in vivo* experiments have in fact been performed, and that the compositions taught by the present disclosure have in fact been administered and achieved the activity and result claimed in the instant claims. Applicants respectfully request the Examiner to review this evidence and acknowledge that this enablement issue has been addressed satisfactorily.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at 301-203-6300 (a local call).

Respectfully submitted,

November 2, 2001

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***Certificate of Mailing by facsimile (37 CFR 1.8)**: I hereby certify that this supplemental response and clean copy of claims is being transmitted to Examiner DeCloux (fax number 703-746-4982) on 2 November 2001.*

William J. Bundren
typed name of person mailing correspondence

Signature of person faxing correspondence

Clean copy of amended/added claims:

12 (twice amended). A method of inducing a thrombus in vivo comprising:
administering a bifunctional binding agent comprising a targeting component and a component that specifically binds platelets;
binding platelets on the binding agent;
inducing activation of the platelets; and thereby
allowing a thrombus to form.

13 (twice amended). The method of claim 12 wherein the targeting component binds to a selected site.

15. CANCELLED

16. CANCELLED

17 (twice amended). The method of claim 12 wherein the component that specifically binds platelets comprises at least one of the components selected from the group consisting of von Willebrand factor, osteopontin, fibrinogen, fibrin, fibronectin, vitronectin, collagen, thrombospondin, laminin, heparin, heparan sulfate, chondroitin sulfate, phospholipase A2, matrix metalloproteinases, thrombin, glass, sialyl-lewis X, fibulin-1, PECAM, ICAM-1, ICAM-2, p-selectin ligand, MAC-1, LFA-1, and portions of any of the above.

18 (twice amended). The method of claim 12 wherein the bifunctional binding agent further comprises a moiety selected from one or more of the following: biotin, homophyllic peptides, and human Fc fragments.

19. (amended) The method of claim 12 wherein the targeting component binds to a ligand/receptor complex.

21 (twice amended). The method of claim 20 wherein the growth factor/growth factor receptor is a VEGF/VEGF receptor.

~~22~~. The method of claim 12 wherein the pre-selected site comprises subendothelium.

~~23~~. The method of claim 12 wherein the pre-selected site comprises tumor-associated antigen.

~~24~~. The method of claim 12 wherein the pre-selected site comprises tumor-specific antigen.

~~25~~. The method of claim 12 wherein the pre-selected site comprises hyperplastic tissue.